



General

Guideline Title

Blood transfusion in the management of sickle cell disease. In: Evidence-based management of sickle cell disease.

Bibliographic Source(s)

Blood transfusion in the management of sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 79-92.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [December 14, 2016 – General anesthetic and sedation drugs](#) : The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains. Consistent with animal studies, recent human studies suggest that a single, relatively short exposure to general anesthetic and sedation drugs in infants or toddlers is unlikely to have negative effects on behavior or learning. However, further research is needed to fully characterize how early life anesthetic exposure affects children's brain development.

Recommendations

Major Recommendations

Definitions of the grades of recommendation (Strong, Weak), the quality of supporting evidence (High, Moderate, Low, Very Low), and consensus statements are presented at the end of the "Major Recommendations" field.

Note from the National Heart, Lung, and Blood Institute (NHLBI) and the National Guideline Clearinghouse (NGC): The evidence-based

management of sickle cell disease (SCD) has been divided into five topic areas with individual summaries covering recommendations to assist health care professionals in various aspects of management. In addition to the current summary, the following are available:

- [Health maintenance for people with sickle cell disease](#)
- [Managing acute complications of sickle cell disease](#)
- [Managing chronic complications of sickle cell disease](#)
- [Hydroxyurea therapy in the management of sickle cell disease](#)

Indications for Transfusion

Key Question 25

In patients with SCD undergoing surgical procedures, does a particular perioperative transfusion approach (simple or exchange transfusion to achieve a predetermined hemoglobin level or percentage of sickle hemoglobin [HbS]) reduce perioperative mortality and complications?

Recommendations

1. In adults and children with sickle cell anemia (SCA), transfuse red blood cells (RBCs) to bring the hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia. (Strong Recommendation, Moderate-Quality Evidence)
2. In patients with homozygous hemoglobin SS (HbSS) disease who require surgery and who already have a hemoglobin level higher than 8.5 g/dL without transfusion, are on chronic hydroxyurea therapy, or who require high-risk surgery (e.g., neurosurgery, prolonged anesthesia, cardiac bypass), consult a sickle cell expert for guidance as to the appropriate transfusion method. (Strong Recommendation, Low-Quality Evidence)
3. In adults and children with hemoglobin SC disease (HbSC) or HbS β^+ -thalassemia, consult a sickle cell expert to determine if full or partial exchange transfusion is indicated before a surgical procedure involving general anesthesia. (Moderate Recommendation, Low-Quality Evidence)

Recommendations for Acute and Chronic Transfusion Therapy

The following tables summarize the expert panel's recommendations for transfusion therapy in acute and chronic complications.

Acute Complications—Graded Recommendations to Transfuse

Indication	How to Transfuse	Quality of Evidence	Strength of Recommendation
Symptomatic acute chest syndrome (ACS) combined with a decreased Hb of 1 g/dL below baseline	Simple transfusion	Low	Weak
Symptomatic severe ACS (as defined by an oxygen saturation less than 90% despite supplemental oxygen)	Exchange transfusion	Low	Strong
Acute splenic sequestration plus severe anemia	Simple transfusion	Low	Strong
Stroke	Simple or exchange transfusion	Low	Moderate

Acute Complications—Consensus Recommendations to Transfuse

Indication	How to Transfuse
Hepatic sequestration	Exchange or simple transfusion
Intrahepatic cholestasis	Exchange or simple transfusion
Multisystem organ failure (MSOF)	Exchange or simple transfusion
Aplastic crisis	Simple transfusion
Symptomatic anemia (see the NGC summary of the NHLBI guideline Managing acute complications of sickle cell disease)	Simple transfusion

Indication	How to Transfuse
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Acute Complications—Graded Recommendations When Transfusion Is Not Indicated

Indication	Quality of Evidence	Strength of Recommendation
Uncomplicated painful crisis	Low	Moderate
Priapism	Low	Moderate

Acute Complications—Consensus Recommendations When Transfusion Is Not Indicated

Indication
<ul style="list-style-type: none"> Asymptomatic anemia Acute kidney injury, unless multiple system organ failure (MSOF)

Chronic Complications—Graded Recommendations for When to Initiate a Chronic Transfusion Program

Indication	How to Transfuse	Quality of Evidence	Strength of Recommendation
Child with transcranial Doppler (TCD) reading* >200 cm/sec	Exchange or simple transfusion	High	Strong
Adults and children with previous clinically overt stroke	Exchange or simple transfusion	Low	Moderate

*TCD reading is the time averaged mean maximal cerebral blood flow velocity. See "Screening for Risk of Stroke Using Neuroimaging" in the NGC summary of the NHLBI guideline [Health maintenance for people with sickle cell disease](#).

Chronic Complications—Graded Recommendations for When Transfusion Is Not Indicated

Indication	Quality of Evidence	Strength of Recommendation
Recurrent splenic sequestration	Low	Weak

Appropriate Management/Monitoring

Key Question 26

In patients with SCA who require RBC transfusion, what are the most effective transfusion protocols that reduce transfusion complications (including a transfusion goal, phenotype-matching monitoring approaches, procedures, or strategies)?

Recommendations

1. RBC units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens. (Moderate Recommendation, Low-Quality Evidence)
2. In patients with SCA, who are not chronically transfused and who are therefore at risk for hyperviscosity due to high percentages of circulating HbS-containing erythrocytes, avoid transfusing to a target hemoglobin above 10 g/dL. (Moderate Recommendation, Low-Quality Evidence)
3. In chronically transfused children with SCA, the goal of transfusion should be to maintain a HbS level of below 30 percent immediately prior to the next transfusion. (Moderate Recommendation, Moderate-Quality Evidence)
4. The expert panel recommends that clinicians prescribing chronic transfusion therapy follow an established monitoring protocol. (Moderate Recommendation, Low-Quality Evidence)

Consensus Protocol for Monitoring Individuals on Chronic Transfusion Therapy

The following is a consensus protocol for the initiation and monitoring of patients on chronic transfusion therapy. It is understood that the

recommended testing schedule may not be available to patients everywhere; therefore, this protocol should serve only as a helpful guide for transfusion management.

At Initiation

- Obtain patient treatment history to include locations where prior transfusions were received and any adverse effects.
- Notify the blood bank that the patient being initiated on chronic transfusion therapy has SCD. Ask the blood bank to contact hospitals where the patient reported receiving previous transfusion therapy to obtain transfusion information.
- Obtain a RBC phenotype, type and screen, quantitative measurement of percent normal hemoglobin (HbA) and percent HbS, complete blood count (CBC), and reticulocyte count.
- Inform the patient if he or she is alloimmunized, so that this information can be communicated as part of the patient's self-reported medical history.

Suggested Evaluation Before Each Transfusion

- CBC and reticulocyte count—This procedure is done to help guide the frequency and volume of transfusions. It is expected that, with effective chronic transfusion therapy, the patient's bone marrow will be suppressed and the reticulocyte count should decrease, but the value may rise by the time of the next transfusion.
- Quantitative measurement of percent HbA and percent HbS—This procedure is done to confirm the success of chronic transfusion therapy with achieving the target percent of HbS.
- Type and screen—This is done to assess whether the patient has developed any new RBC antibodies from the prior transfusion.

Suggested Periodic Evaluations

- Liver function tests annually or semiannually—These tests are done to follow liver function in individuals with iron overload.
- Serum ferritin (SF) quarterly—This test is done to follow iron stores in individuals with iron overload; it can be helpful in evaluating compliance with chelation.
- Screening for hepatitis C, hepatitis B, and human immunodeficiency virus (HIV) annually.
- Evaluation for iron overload every 1–2 years by validated liver iron quantification methods such as liver biopsy, magnetic resonance imaging (MRI) R2 or MRI T2* or R2* techniques.

Complications of Transfusions

Key Question 27

In patients with SCD requiring transfusion, what are the most effective strategies to reduce the risk of alloimmunization or autoimmunization?

Key Question 28

In patients with SCD undergoing chronic transfusion therapy, what are the effective strategies to reduce iron overload, and what are the most accurate diagnostic tests to estimate iron overload?

Key Question 29

In patients with SCD undergoing transfusion therapy, what are the most effective strategies to reduce the risk of hemolysis?

Key Question 30

In patients with SCD undergoing transfusion therapy, what are the most effective strategies to prevent and treat transfusion-associated hyperviscosity?

Recommendations for the Management and Prevention of Transfusion Complications

Recommendations for Both Children and Adults

1. Obtain patient transfusion history to include locations of prior transfusions and adverse effects. (Consensus–Panel Expertise)
2. Ask the blood bank to contact hospitals where patient reported receiving previous transfusion therapy to obtain transfusion information. (Consensus–Panel Expertise)
3. RBC units that are to be transfused to individuals with SCD should include matching for C, E, and K antigens. (Moderate Recommendation, Low-Quality Evidence)
4. Consult the blood bank for a workup of a possible delayed hemolytic transfusion reaction (DHTR) in a patient with any of the following

signs or symptoms: acute anemia, pain, or jaundice within 3 weeks after a blood transfusion. (Strong Recommendation, Moderate-Quality Evidence)

5. In patients with SCA who are not chronically transfused and who are therefore at risk for hyperviscosity, avoid transfusing to a target hemoglobin above 10 g/dL (unless the patients are already on chronic transfusions or have low percent HbS levels). (Moderate Recommendation, Low-Quality Evidence)
6. In patients who receive chronic transfusion therapy, perform serial assessment of iron overload to include validated liver iron quantification methods such as liver biopsy, or MRI R2 or MRI T2* and R2* techniques. The optimal frequency of assessment has not been established and will be based in part on the individual patient's characteristics. (Strong Recommendation, Moderate-Quality Evidence)
7. Administer iron chelation therapy, in consultation with a hematologist, to patients with SCD and with documented transfusion-acquired iron overload. (Moderate Recommendation, Moderate-Quality Evidence)

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Strong recommendation High-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies*	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation Moderate-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation Low-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation Very low-quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.
Weak recommendation High-quality evidence	Benefits closely balanced with harms and burdens	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation Moderate-quality evidence	Benefits closely balanced with harms and burdens	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation Low-quality evidence	Uncertainty in the estimates of benefits, harms, and burdens; benefits may be closely balanced with harms and burdens	Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation	Major uncertainty in the estimates of benefits,	Evidence for at least one critical outcome from unsystematic clinical	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical

Grade of Recommendation Very low-quality evidence	Clarity of Risk/Benefit harms, and burdens: benefits may or may not be balanced with harms and burdens	Quality of Supporting Evidence observations or very indirect evidence	Implications outcome is very uncertain.

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*Exceptionally strong evidence from unbiased observational studies includes: (1) evidence from studies that yield estimates of the treatment effect that are large and consistent; (2) evidence in which all potential biases may be working to underestimate an apparent treatment effect, and therefore, the actual treatment effect is likely to be larger than that suggested by the study data; and (3) evidence in which a dose-response gradient exists.

Consensus Statements

The panel believed that, for this guideline document to be most helpful to primary care providers and specialty health care professionals, it needed to be comprehensive. This required that, in areas with minimal existing direct evidence, the panel would provide recommendations based on their and others' expert opinions. Those recommendations are labeled as "consensus." Several different situations, outlined below, led to the use of consensus statements.

Consensus—Panel Expertise

- Systematic reviews conducted by the methodology team revealed minimal or no supporting evidence (e.g., management of acute hepatic sequestration).
- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with SCD presenting with fever or worsening anemia).
- Recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus—Adapted

- These recommendations were based on the panel's expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Sickle cell disease (SCD)

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Nephrology

Nursing

Pediatrics

Surgery

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To synthesize the available scientific evidence on sickle cell disease (SCD) and offer guidance to busy primary care clinicians
- To help people living with SCD receive appropriate care by providing the best science-based recommendations to guide practice decisions
- To assist health care professionals in the management of common issues, including routine health maintenance, the recognition and treatment of common acute and chronic complications and comorbidities of SCD, as well as the indications for and monitoring of hydroxyurea and blood transfusion therapy
- To help provide the latest evidence-based recommendations to manage this condition and to help engage health care professionals in supporting their implementation at the practice level
- To present evidence-based recommendations that summarize the indications, risks, and benefits of erythrocyte transfusion therapy in SCD

Target Population

Infants, children, adolescents, and adults with sickle cell disease (SCD)

Interventions and Practices Considered

1. Perioperative blood transfusion (simple or exchange transfusion)
2. Transfusion therapy (simple or exchange) for acute and chronic complications of sickle cell disease (SCD)
3. Phenotype matching
4. Targeting hemoglobin levels
5. Establishing a transfusion monitoring protocol (at initiation, before each transfusion, and periodic evaluations)
6. Preventing and managing complications of transfusion therapy

Major Outcomes Considered

- Complication-specific outcomes including resolution of complication

- General sickle cell disease (SCD) outcomes if relevant:
 - Death
 - Stroke
 - Pain crises
 - Need for transfusion
 - Hemoglobin and hemoglobin F levels
 - Hemoglobin S concentration
- Outcomes of diagnostic studies: accuracy of diagnosis if reported

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

General Literature Search

Due to the comprehensive scope of the guidelines, the search strategies for the systematic reviews were designed to have high sensitivity and low specificity; hence, the strategies were often derived from population and condition terms (e.g., people with sickle cell disease [SCD] who have priapism) and not restricted or combined with outcome or intervention terms. To be inclusive of the available literature in the field, searches included randomized trials, nonrandomized intervention studies, and observational studies. Case reports and small case series were included only when outcomes involved harm (e.g., the adverse effects of hydroxyurea) or when rare complications were expected to be reported.

Literature searches involved multiple databases (e.g., Medline® In-Process & Other Non-Indexed Citations, MEDLINE®, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature [CINAHL®], TOXLINE®, and Scopus) and used controlled vocabulary (prespecified) terms supplemented with keywords to define concept areas.

An updated search was performed to span the time from June 1, 2010 through July 11, 2014.

Guideline-specific Literature Search

A comprehensive study of several databases was conducted, and all human studies in English published from 1970 to July 2010 that addressed each Patient, Intervention, Comparison, Outcomes, and Study Design (PICOS) question were identified. In some cases in this guideline, a literature search was not conducted or the search yielded no evidence (e.g., management of hyperviscosity), so the expert panel relied on their cumulative expertise and knowledge to make recommendations; these recommendations are labeled "Consensus-Panel Expertise."

Detailed information on the search questions, search strategy, study selection process, and list of excluded studies used in this guideline can be found in the systematic review (see the "Availability of Companion Documents" field).

Number of Source Documents

General Literature Search

The initial literature searches performed to support these guidelines yielded 12,532 references. The expert panel also identified an additional 1,231 potentially relevant references. An updated search of randomized controlled trials (RCTs) added eight trials. All abstracts were reviewed independently by two reviewers using an online reference management system (DistillerSR—<http://systematic-review.net>) until reviewers reached adequate agreement (kappa ≥ 0.90). A total of 1,575 original studies were included in the evidence tables.

Guideline-specific Literature Search

A total of 300 studies were included.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

See the "Rating Scheme for the Strength of the Recommendations" field.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

General Methodology

Evidence Synthesis

Methodologists developed evidence tables to summarize individual study findings and present the quality of evidence (i.e., confidence in the estimates of effect). The tables included descriptions of study population, sickle cell disease (SCD) genotypes, interventions, and outcomes. Additional methodological details are discussed in each evidence table, including the search question, search strategy, study selection process, and list of excluded studies (see the "Availability of Companion Documents" field).

Evidence Framework

The methodology team used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to grade the quality of evidence, and, in concert with the panel, determine the strength of recommendations. The GRADE framework is accepted by more than 75 national and international organizations (see exhibit 3 in the original guideline document). It provides the advantages of: (a) separately judging the quality of supporting evidence and strength of recommendations, and (b) incorporating factors other than evidence in decisionmaking (e.g., the balance of benefits and harms; the perceived values and preferences of those with SCD; resources; and clinical and social context). GRADE emphasizes the use of patient-important outcomes (i.e., outcomes that affect the way patients feel, function, or survive) over laboratory and physiologic outcomes.

Determining Evidence Quality

In the GRADE framework, the quality of evidence (in this case, the body of evidence) is rated as high, moderate, low, or very low. The quality of evidence derived from randomized trials starts as "high," and the quality of evidence derived from observational studies starts as "low." The quality of evidence can then be lowered due to methodological limitations in individual studies (risk of bias), inconsistency across studies (heterogeneity), indirectness (the extent to which the evidence fails to apply to the specific clinical question in terms of the patients, interventions, or outcomes), imprecision (typically due to a small number of events or wide confidence intervals), and the presence of publication and reporting biases. Conversely, the quality of evidence can be upgraded in certain situations such as when the treatment effect is large or a dose-response relationship is evident.

Existing Systematic Reviews and Clinical Practice Guidelines

The expert panel and methodology team identified existing systematic reviews and clinical practice guidelines that were relevant to the topics of this guideline, even though they were not necessarily specific to people with SCD. If the methodological quality of these resources was found to be appropriate by the methodology team, they were used. Using this external evidence was considered helpful because well-conducted systematic reviews made the process of identifying relevant studies more feasible. In addition, using existing guidelines developed by professional organizations enabled the panel to develop more comprehensive recommendations that addressed specific aspects of care in individuals with SCD. Usually, this external evidence was derived from studies in non-sickle cell patient cohorts because it was felt that they offered more precise and useful inferences than evidence derived from sickle cell patient studies. For example, comparative evidence in the area of pain management in people with SCD was sparse. In this situation, pain management guidelines from individuals with other pain-related conditions proved to be helpful.

The methodology team used the AMSTAR tool to assess the methodological quality of systematic reviews. Recent well-conducted systematic reviews were identified that addressed hydroxyurea therapy in pediatric and adult patients. The expert panel and methodology team appraised these reviews and conducted additional searches to update the existing systematic review through May 2010 to find evidence for the benefits, harms, and barriers of using hydroxyurea. Regarding the management of children with SCD complications, the panel also used recent evidence that had been systematically reviewed.

Existing clinical practice guidelines were considered acceptable if they had prespecified clinical questions, were developed after a comprehensive literature search, had explicit and clear criteria for the inclusion of evidence, and included recommendations that were explicitly linked to the quality of supporting evidence. The expert panel and methodology team used relevant recommendations from the U.S. Preventive Services Task Force (USPSTF), the Advisory Committee on Immunization Practices (ACIP), the Centers for Disease Control and Prevention's (CDC) adaptation of the World Health Organization's (WHO) "Medical Eligibility Criteria for Contraceptive Use," and the American Pain Society's "Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease," and "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain."

Guideline-specific Methodology

Detailed information on the evaluated studies as well as the observational and case studies/series referenced can be found in the evidence table in the systematic review (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These guidelines were developed by an expert panel composed of health care professionals with expertise in family medicine, general internal medicine, adult and pediatric hematology, psychiatry, transfusion medicine, obstetrics and gynecology, emergency department nursing, and evidence-based medicine. Panel members were selected by the National Heart, Lung, and Blood Institute's (NHLBI's) leadership.

Process and Methodology

The expert panel first convened in the spring of 2009 to establish the vision and purpose of the panel, discuss the process and schedule for producing the guidelines, and determine the critical areas to be addressed. Prior to this meeting, the expert panel participated in a conference call to introduce the panel's work and discuss the overarching questions that should be answered by the guidelines. Before beginning the writing of the guidelines report, the expert panel divided its work into sections dealing with preventive care or health maintenance, recognition and management of acute sickle-cell disease (SCD)-related complications, recognition and management of chronic SCD-related complications, and the two most broadly assessed and available disease-modifying therapies for SCD, hydroxyurea and chronic blood transfusions.

With the assistance of the methodology team and the supporting evidence center, the panel then developed key questions and literature search terms to identify evidence. The field of SCD has a limited number of randomized controlled trials (RCTs) or large prospective cohort studies to guide clinical decisionmaking; therefore, few of the recommendations in this document are based on this highest quality evidence. For common health issues, the panel included the evidence-based recommendations of the United States Preventive Services Task Force (USPSTF) as well as vetted recommendations of other groups. These recommendations include the SCD reproductive-related recommendations of the World Health Organization (WHO), the immunization recommendations of the Advisory Committee on Immunization Practices (ACIP), and the acute and chronic pain management recommendations of the American Pain Society (APS). These recommendations are denoted as "Consensus-Adapted."

Recognizing the need to provide practical guidance for common problems that may lie outside of the panel's evidence reviews or available science, in many areas the published evidence was supplemented by the expertise of the panel members, who have many years of experience in managing and studying individuals with SCD. Recommendations based on the opinions of the expert panel members are labeled as "Consensus-Panel Expertise." Each is clearly labeled with the strength of the recommendation and the quality of evidence available to support it.

Determining the Strength of Recommendations

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework rates the strength of recommendations as "strong" or "weak." However, the panel modified the GRADE system and used a third category—moderate—when they determined that patients would be better off if they followed a recommendation, despite there being some level of uncertainty about the magnitude of benefit of the

intervention or the relative net benefit of alternative courses of action. The panel intends for these moderate-strength recommendations to be used to populate protocols of care and provide a guideline based on the best available evidence. The panel does not intend for weak- or moderate-strength recommendations to generate quality-of-care indicators or accountability measures or affect insurance reimbursement. Variation in care in the areas of weak- or moderate-strength recommendations may be acceptable, particularly in ways that reflect patient values and preferences. Conversely, strong recommendations represent areas in which there is confidence in the evidence supporting net benefit, and the recommendations likely apply to most individuals with sickle cell anemia. For more information, see the "Rating Scheme for the Strength of the Recommendations" field.

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Recommendations

Grade of Recommendation	Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications
Strong recommendation High-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Consistent evidence from well-performed randomized controlled trials (RCTs) or exceptionally strong evidence from unbiased observational studies*	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation Moderate-quality evidence	Benefits clearly outweigh harms and burdens, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence), or unusually strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an impact on confidence in the estimate of effect and may change the estimate.
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Strong recommendation Very low-quality evidence (very rarely applicable)	Benefits clearly outweigh harms and burdens, or vice versa	Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect, for at least one critical outcome, is very uncertain.
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Weak recommendation Very low-quality	Major uncertainty in the estimates of benefits, harms, and burdens; benefits may or may not	Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain.

evidence Grade of Recommendation	be balanced with harms and burdens Clarity of Risk/Benefit	Quality of Supporting Evidence	Implications

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Consensus Statements

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Consensus—Panel Expertise

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- An adequate systematic review of the literature was not feasible because of anticipated low yield or no yield (e.g., comparative effectiveness of management approaches for individuals with sickle cell disease [SCD] presenting with fever or worsening anemia).
- Recommendations were based on the panel's expert knowledge, practice experience, and ability to extrapolate evidence from non-SCD populations (e.g., management of chronic opioid therapy in chronic SCD pain).

Consensus—Adapted

- These recommendations were based on the panel's expert knowledge to adapt recommendations derived from existing guidelines and synthesized evidence developed by other professional societies (e.g., management of acute and chronic pain in SCD). The panel clearly identified these statements as consensus recommendations and acknowledges that these areas represent gaps in the evidence base and areas for future research.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Prior to publication, these guidelines were reviewed by the National Heart, Lung, and Blood Institute (NHLBI) Advisory Council, a separate panel of sickle cell disease (SCD) experts, and the National Blood Disorders Program Coordinating Committee. The guidelines were also posted to the NHLBI Web site for an extensive public review and comment period, which resulted in the submission of more than 1,300 comments from individuals and professional societies. The expert panel and NHLBI staff reviewed each comment or recommendation, many of which resulted in a revision to the guidelines. The guidelines were then reviewed by SCD experts representing three professional societies.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Red blood cell transfusions can help ameliorate many of the acute and chronic complications of sickle cell disease (SCD) and, at times, can be life-saving.
- Three benefits of exchange transfusion, related primarily to the removal of recipient sickle erythrocytes, include (1) increasing the percent of normal (donor) hemoglobin (HbA)-containing erythrocytes remaining after transfusion; (2) permitting transfusion of increased volumes of donor blood without increasing the hematocrit to levels that excessively increase blood viscosity; and (3) reducing the net transfused volume, which reduces iron overload.

Potential Harms

- Many of the recognized hazards of transfusion, such as the risk of alloimmunization, are amplified in sickle cell disease (SCD); therefore, decisions to utilize transfusion therapy in SCD must be based on risk-benefit assessments.
- Although red blood cell (RBC) transfusions can help ameliorate many of the acute and chronic complications of SCD—and, at times, can be life-saving—their administration is associated with a wide variety of complications. Some transfusion-associated events are relatively mild, while others can be severe or even fatal. Health care providers should become familiar with the range of transfusion complications and learn their signs and symptoms as well as appropriate diagnostic testing, prevention strategies, and therapeutic interventions when warranted. Refer to the section "Complications of Transfusions" in the original guideline document for a discussion of these complications, including alloimmunization and autoimmunization, iron overload, hemolysis, and hyperviscosity.

Qualifying Statements

Qualifying Statements

The purpose of the "Evidence-Based Management of Sickle Cell Disease: Expert Panel Report (EPR), 2014" is to synthesize the available scientific evidence on sickle cell disease and offer guidance to busy primary care clinicians. Readers of this report should remember that this document is intended to provide guidance for management, not to be rigidly prescriptive. The panel recognizes that the responsible clinician's judgment regarding the management of patients remains paramount. Therefore, the Expert Panel Report is a tool to be adopted and implemented in local and individual settings, and to provide an opportunity for shared decisionmaking in which providers and patients are both fully engaged.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Blood transfusion in the management of sickle cell disease. In: Evidence-based management of sickle cell disease. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. p. 79-92.

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014

Guideline Developer(s)

National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]

Source(s) of Funding

United States Government

Guideline Committee

Expert Panel

Composition of Group That Authored the Guideline

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Refer to the original guideline document for members of the National Heart, Lung, and Blood Institute staff and the contractor support.

Financial Disclosures/Conflicts of Interest

The National Heart, Lung, and Blood Institute (NHLBI) established the expert panel and invited the panel members. All members served as volunteers and received no compensation from NHLBI or any other entity for their participation.

During the development of these guidelines, measures were taken to ensure the transparency of the evidence review process and to manage all potential or perceived conflicts of interest. At the initial expert panel meeting, expert panel members were asked by the panel co-chairs to disclose interests and relationships that could potentially influence their participation or pose a potential conflict of interest. The responses are provided below.

- Araba N. Afenyi-Annan, M.D., M.P.H.—Consultant, Transfusion Safety Summit: Risks Associated with Iron Toxicity in Transfusional Medicine—Novartis Pharmaceuticals Corporation (November 2008); Duke University Comprehensive Sickle Cell Center, Mentored Research Training Supplement (April 2005–April 2006); Expert Witness for Hall, Booth, Smith & Slover, P.C. (2010–present)
- Samir K. Ballas, M.D.—Speaker's Bureau, Novartis; Sickle Cell Advisory Board, HemaQuest; U.S. Sickle Cell Advisory Board, Sangart
- Kathryn L. Hassell, M.D.—Advisory Board, ApoPharma; Consultant, AGA Medical Corp.; Consultant and Principal Investigator of Local Site Multicenter Sickle Cell Study, Terumo, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, GlycoMimetics, Inc.; Principal Investigator of Local Site Multi-Center Sickle Cell Study, Emmaus, Inc.; Board of Directors, Mount Evans Home Health & Hospice; Medical Advisory Board, Foundation for Women and Girls with Blood Disorders; Medical Advisory Board, PFO Research Foundation
- Andra H. James, M.D., M.P.H.—Consultancy for the von Willebrand Disease Medical Advisory Board for CSL Behring; Research study of antithrombin levels in pregnancy for Grifols/Talecris; Study of von Willebrand factor levels and fibrinogen levels post partum for CSL Behring; Expert witness for Johnson & Johnson and Sanofi-Aventis
- Lanetta Jordan, M.D., M.P.H., M.S.P.H.—National Heart, Lung, and Blood Advisory Council; Faculty Chair, Sickle Cell Disease Association of America, Inc. (SCDAA) and National Initiative for Children's Healthcare Quality (NICHQ) for Health Resources and Services Administration-funded Sickle Cell Disease Treatment Demonstration Program; AESRx Medical Advisory Council; Prolong Pharmaceutical Medical Advisory Board; Consultant for NKT Therapeutics, TriStem, Pfizer, and Novartis; Board Member, Foundation for Women and Girls with Blood Disorders and Miami YWCA
- Sophie M. Lanzkron, M.D., M.H.S.—Scientific Advisory Board for HemaQuest; Principal investigator on studies sponsored by Emmaus, GlycoMimetics, Inc., and Novartis
- Paula J. Tanabe, Ph.D., R.N., M.S.N., M.P.H.—Partner, ESI Triage Research Team, LLC; Principal investigator on Agency for Healthcare Research and Quality research grant; Subcontractor to the Michigan Public Health Institute and the Health Resources and Services Administration (HRSA) to conduct a project in SCD, pediatrics, emergency department (ED) research; recipient of Duke School of Nursing grant to complete a project to measure the effect of a high dose opioid protocol to treat adults with a vaso-occlusive crisis (VOC) in the ED; Expert witness consultant on one SCD legal case
- Russell E. Ware, M.D., Ph.D.—Consultant for Bayer, Novartis Pharmaceuticals, and Sobi

No relationships to disclose: George R. Buchanan, M.D.; Richard Lottenberg, M.D.; William J. Savage, M.D., Ph.D.; Barbara P. Yawn, M.D., M.Sc., M.S.P.H.

Guideline Endorser(s)

American Academy of Emergency Medicine - Medical Specialty Society

American Academy of Pediatrics - Medical Specialty Society

American Academy of Physician Assistants - Professional Association

American Osteopathic Association - Professional Association

American Society of Hematology - Medical Specialty Society

American Society of Pediatric Hematology/Oncology - Professional Association

International Association of Sickle Cell Nurses and Physician Assistants - Professional Association

National Black Nurses Association, Inc - Professional Association

National Institute for Children's Health Quality - Professional Association

National Medical Association - Professional Association

Sickle Cell Disease Association of America - Disease Specific Society

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [National Heart, Lung, and Blood Institute \(NHLBI\) Web site](#) .

Print copies: Available from the NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com

Availability of Companion Documents

The following are available:

- Evidence-based management of sickle cell disease. Expert panel report quick guide. Bethesda (MD): National Heart, Lung, and Blood Institute (NHLBI); 2014. 45 p. Electronic copies: Available the [National Heart, Lung, and Blood Institute \(NHLBI\) Web site](#) .
- Management of sickle cell disease. Summary of the 2014 evidence-based report by expert panel members. JAMA. 2014 Sep 10;312(10):1033-1048. Electronic copies: Available from the [Journal of the American Medical Association \(JAMA\) Network Web site](#) .
- Murad MH, Hazem A, Shahrour A, Prokop L, Lane M, Mullan R, Montori VM. Transfusion in sickle cell disease: a systematic review of benefits, complications, and management of complications, 2012. 243 p. Electronic copies: Available from the [NHLBI Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 24, 2014. This summary was updated by ECRI Institute on February 15, 2017 following the U.S. Food and Drug Administration advisory on general anesthetic and sedation drugs.

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